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(54) Process for manufacturing suspension preparations of automatic injection type
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(56) Cited Literatures
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Japanese Patent Publication No. 1952-3222 (JP, B1)
Japanese Patent Publication No. 1961-19125 (JP, B1)
Japanese Patent Publication No. 1961-19379 (JP, B1)
Cited Publication
Yohkichi Arai and Others, Metal Soaps, Expanded Edition (Zoho Kinzoku Sekken), page 234, Published on September 1, 1952, Published by Sangyou Tosho Kabushiki Kaisha

Detailed Description of the Invention

The present invention relates to a process for manufacturing stable suspension preparations of automatic injection type.

There have been heretofore known the following examples as processes for suspending a solid pharmaceutical ingredient, which is insoluble or sparingly soluble in a liquefied propellant, in the liquefied propellant.

These examples include a process by the use of a non-ionic surface active agent (Japanese Patent Publication No. 1961-14397), a process by the use of a lecithin, lanolin, cholesterol or a derivative thereof and a higher fatty acid ester of a lower alcohol (Japanese Patent Publication No. 1965-28956), a process by the use of an anionic surface active agent of the alkylsulfonic acid series (Japanese Patent Publication No. 1966-10032), a process by the use of a surface active agent of the phosphate type (Japanese Patent Publication No. 1968-25567) and the like. However, the suspension preparations obtained by any of these processes induce sedimentation, floatation, aggregation or the like of the suspended, solid pharmaceutical ingredient, thereby having not yet been resulted in a sufficiently satisfactory result.

As a result of carrying out a variety of studies in order to obtain suspension preparations of automatic injection type that do not have such defects, the present inventors have found that, in the case where a metal salt of a fatty acid is used as the suspending agent, extremely stable, suspension preparations of automatic injection type can be obtained by the usage thereof in a very small amount as compared with the usage amount of a conventional suspending agent.

In other words, the present invention relates to a process for manufacturing suspension preparations of automatic injection type, which is characterized by mixing a micronized, solid pharmaceutical ingredient, which is insoluble or sparingly soluble in a liquefied propellant, with a metal salt of a fatty acid, for example, such as the aluminium salt, the calcium salt, the magnesium salt and the zinc salt, dissolved singly or as a mixture of some or all of them in an oil-soluble solvent, followed by suspending the resulting mixture in the liquefied propellant.

The fatty acid component in the fatty acid salt to be used in the present invention includes a straight-chained fatty acid having the carbon number of C_6 to C_{20}, a branched-chain fatty acid, a substituted fatty acid substituted with the hydroxyl group or the like, and the like. Accordingly, the examples of the fatty acid salt to be used in the present invention include aluminum distearate, aluminum tristearate, aluminum 12-hydroxystearate, calcium stearate, magnesium oleate, zinc isostearate and the like.

As for the oil-soluble solvent, any solvent, which is capable of dissolving the above-mentioned metal salt of fatty acid, can be employed. Examples to be used singly or in a mixture include isostearic acid, 2-octyldodecanol, 2-hexadecanol, isopropyl myristate, trioleyl phosphate, diethylene glycol, diethyl ether and the like.

As for the liquefied propellant, all of the conventionally used propellants can be used singly or in a mixture. Examples to be used include a lower alkane such as butane, pentane or the like, a lower alkyl chloride such as methyl chloride, a fluorinated or chlorinated, lower alkane such as dichlorodifluoromethane, dichlorotetrafluoromethane, trichloromonofluoromethane or the like, and the like.

As for the solid pharmaceutical ingredient, any of solids, which are insoluble or sparingly soluble in a liquefied propellant, can be employed. Some of them are

exemplified, for example, by lysozyme chloride, thiamphenicol, hydrocortisone, isopretenol sulfate and the like.

The smaller is the particle size of the pharmaceutical ingredient the better, where the particle size of about 1 to 25 μm is usually preferred. The pharmaceutical ingredient is contained in about 0.01 to 20% (by weight) of the total weight of the composition, desirably in about 0.01 to 3.0% (by weight). The above-mentioned metal salt of fatty acid is used in an amount of 0.0005 to 1.0% (by weight), but may be used in an amount more or less than this range, as needed. The use in an amount of 0.001 to 0.05% (by weight) is most preferred.

The suspension preparations to be obtained according to the process of the present invention do not induce a phenomenon such as sedimentation, floatation, aggregation or the like of the suspended, solid pharmaceutical ingredient even after standing for a long period.

The present invention is embodied in more detail by the following examples.

Example 1

In 0.3 g of trioleyl phosphate was dissolved with heating 0.01 g of calcium 12-hydroxystearate, and into the resulting solution was mixed after cooling 0.5 g of a lysozyme chloride powder that was milled to about 5 to 20 μm. Then, the resulting stock mixture was placed in an aerosol container, into which was sealed a mixture of Freon 12 (dichlorodifluoromethane) and Freon 11 (trichloromonofluoromethane) in an equivalent amount, thereby making the weight of the content 20 g.

Example 2

Into 0.01 g of calcium isostearate was mixed 0.5 g of a lysozyme chloride powder, and, then, the resulting mixture was subjected to an operation similar to that in Example 1, thereby making the weight of the content 20 g.

Example 3

In 2.0 g of isostearic acid was dissolved with heating 0.005 g of aluminum distearate, and into the resulting solution was mixed after cooling 0.5 g of a lysozyme chloride powder that was milled to about 5 to 20 μm. Then, the resulting mixture was subjected to an operation similar to that in Example 1, thereby making the weight of the content 20 g.

Example 4

In 2.0 g of 2-octyldodecanol was dissolved with heating 0.005 g of aluminum monostearate, and into the resulting solution was mixed after cooling 0.025 g of hydrocortisone that was milled to about 5 to 20 μm. Then, the resulting mixture was subjected to an operation similar to that in Example 1, thereby making the weight of the content 20 g.

Example 5

In 0.2 g of isopropyl myristate was dissolved with heating 0.01 g of calcium isostearate, and into the resulting solution was mixed after cooling 0.04 g of isopretenol sulfate that was milled to about 5 to 20 μm. Then, the resulting stock mixture was placed in an aerosol container, into which was sealed a mixture (30 : 70) of Freon 12 (dichlorodifluoromethane) and Freon 114 (dichlorotetrafluoromethane), thereby making the weight of the content 20 g.

Example 6

In 2.5 g of trioleyl phosphate were dissolved with heating 0.005 g of aluminum monostearate and 0.005 g of calcium 12-hydroxystearate, and into the resulting solution was mixed after cooling 0.2 g of a thiamphenicol powder that was milled to 1 to 25 μm. Then, the resulting mixture was subjected to an operation similar to that in Example 1, thereby making the weight of the content 20 g.

In the following are described the experimental results with regard to the suspension stability of the suspension preparations of automatic injection type of the present invention.

Formulation examples 1 to 3 in the following table correspond to the formulations according to Examples 1 to 3, respectively. Formulation examples 4 to 6, in which conventional suspending agents were used, were chosen as the controls. Formulation examples 4 to 6 represent the formulations in which calcium isostearate in Example 2 was replaced for compounding by 0.1 g of trioleyl phosphate, 0.2 g of sorbitan trioleate and 0.04 g of yolk lecithin, respectively.

The suspended time represents the measurement of a time during which a uniform suspended state was maintained in appearance after standing of the mixture obtained by shaking each of the formulations to make a suspended state.

Formulation example	Suspending agent	Suspended time (minutes)
1	Calcium 12-hydroxystearate	160
2	Calcium isostearate	160
3	Aluminum distearate	360
4	Trioleyl phosphate	7
5	Sorbitan trioleate	11
6	Yolk lecithin	5

As shown in the above-mentioned table, the suspension preparations of automatic injection type of the present invention are superior in the suspensibility than those in which the heretofore-known suspending agents are used.

Moreover, in control examples 4 to 6, caking occurred after a long-term storage, resulting in precipitation of a solid material at the bottom, which could not give rise to a uniform suspension by re-shaking, whereas such a case did not occur in the preparations of the present invention.

[57] What Is Claimed Is

1. A process for manufacturing suspension preparations of automatic injection type, which is characterized by mixing a micronized, solid pharmaceutical ingredient, which is insoluble or sparingly soluble in a liquefied propellant, with the aluminum salt, the calcium salt, the magnesium salt and the zinc salt of a fatty acid, dissolved singly or as a mixture of some or all of them in an oil-soluble solvent, followed by suspending the resulting mixture in the liquefied propellant.